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Title of project: Identification of Gene Regulatory Mechanisms Controlling Human Intestinal GLP-1 Expression

A**BSTRACT**

Diabetes is one of the fastest-growing health issues worldwide, and in 2019 it was estimated that more than 400 million adults are living with diabetes and the associated risk of developing comorbidities such as cardiovascular disease, retinopathy and nephropathy. In recent years, GLP-1 receptor agonists have been employed therapeutically in the treatment of type 2 diabetes and obesity. GLP-1 is a peptide hormone encoded by the *GCG* gene, and plays critical roles in glycaemic control and satiety. GLP-1 is endogenously produced and secreted by a rare population of enteroendocrine cells, intestinal L-cells, predominantly found in the ileum and colon. At present our knowledge of the mechanisms controlling *GCG* expression and L-cell function is very limited, but an increased understanding of these mechanisms could lead to new therapeutic avenues for treatment of patients with diabetes. Characterisation of cell type-specific gene regulatory enhancer landscapes can provide critical insights into gene regulatory networks controlling *GCG* transcription and L-cell identity, but so far, it

has been difficult to study human GLP-1 expressing L-cells in a physiologically relevant context. With the development of three-dimensional (3D) cell culture systems, human intestinal epithelial cells can now be cultured as self-organising structures (organoids) with a cellular composition and architecture similar to the primary tissue. This advanced organoid culture platform provides a physiological relevant model that upon genetic manipulations can be used for isolation and characterization of the rare human GLP-1 expressing L-cells. Therefore, the aims of this PhD project are firstly to generate genetically modified human intestinal organoids where GLP-1 expressing cells are fluorescently labelled. These cultures will subsequently be used to define the enhancer landscapes controlling L-cell identity and *GCG* expression and to characterise transcriptional regulators controlling *GCG* expression and L-cell biology.The proposed research will provide new insight into the mechanisms that control the production of GLP-1 in enteroendocrine cells. Such knowledge could ultimately have relevance for the development of new therapeutic options for enhancing endogenous GLP-1 secretion. Furthermore, the enhancer map will be used for studies investigating whether genetic susceptibility to metabolic diseases could be linked to L-cell biology.